Autoinflammatory Disorders

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Stefan Berg, Per Wekell, Anders Fasth,
Philip N. Hawkins, and Helen Lachmann

7.1 Introduction

Autoinflammatory disorders are a group of diseases that are characterized by recurrent or continuous, generalized inflammation where no infectious or autoimmune cause can be detected [110, 158]. The term was first used for the Mendelian inherited periodic fever syndromes (Table 7.1).

The concept of autoinflammatory disorders has expanded and now at least 25 separate genes are implicated in the monogenetic diseases (infevers, http://fmf.igh.cnrs.fr/ISSAID/infevers) as well an increasing number of polygenic and multifactorial diseases. (*See Table 1.6 and Fig. 1.13 for updated classification of autoinflammatory disorders*).

S. Berg, MD, PhD (✉)
Department of Pediatrics, University of Gothenburg, The Queen Silvia Children's Hospital, Gothenburg, Sweden

P. Wekell, MD, PhD
Department of Pediatrics, University of Gothenburg, NU-Hospital Group, Uddevalla, Sweden

A. Fasth, MD, PhD
Department of Pediatrics, Institute of Clinical Sciences, University of Gothenburg, Gothenburg, Sweden

P.N. Hawkins, MBBS, PhD, FMedSci
H. Lachmann, MA, MB, BChir, MD, FRCP, FRCPath
Royal Free Hospital London NHS Foundation Trust, Centre for Amyloidosis and Acute Phase Proteins, Division of Medicine, University College London, London, UK

This chapter will mainly focus on the Mendelian inherited autoinflammatory diseases as knowledge in the field has expanded considerably and many of the polygenic and multifactorial diseases are discussed in the rheumatologic and gastroenterology literature. As yet there is not complete consensus on which polygenic and multifactorial diseases are classed as autoinflammatory and this will probably change in the coming years. Autoinflammatory diseases are a consequence of dysregulation of the innate rather than the adaptive immune system. The relationships between adaptive and innate immunity are complex but a classification of immunological diseases according to the extent to which these two systems are involved was proposed by McGonagle and McDermott in 2006 [160] (Fig. 7.1). A new definition of autoinflammatory diseases "clinical disorders marked by abnormally increased inflammation, mediated predominantly by the cells and molecules of the innate immune system, with a significant host predisposition" was introduced in 2010 and thus highlights the importance of the innate immune system [126].

Common symptoms during attacks of autoinflammatory diseases are malaise, fever, skin rash, arthritis/arthralgia, abdominal pain and CNS manifestations. The patients also often have an intense inflammatory reaction during the attacks with elevated white cells counts and biochemical markers of inflammation. Onset of the disease is generally in childhood or adolescence but almost 10 % present as adults (http://www.printo.it/eurofever/). The patients are usually

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Table 7.1 Characteristics of the hereditary periodic fevers

Periodic fever syndrome	Gene	Mode of inheritance	Predominant population	Usual age at onset	Potential precipitants of attacks	Distinctive clinical features	Typical duration of attacks	Typical frequency of attacks	Characteristic laboratory abnormalities	Treatment
FMF	*MEFV* Chromosome 16	Autosomal recessive (dominant in some families)	Eastern Mediterranean	Childhood/ early adulthood	Usually none, Occasionally menstruation, fasting, stress, or trauma	Short severe attacks Erysipelas-like erythema	½–3 days	Variable	Marked acute phase response during attacks	Colchicine (Anti-IL-1 therapies in resistant cases)
TRAPS	*TNFRSF1A* Chromosome 12	Autosomal dominant	Northern European, but reported in many ethnic groups	Childhood/ early adulthood	Usually none	Prolonged symptoms	More than a week (may be very prolonged)	Variable (may be continuous)	Marked acute phase response during attacks Low levels of soluble TNFR1 when well	Anti IL-1 therapies Etanercept, High-dose corticosteroids
MKD/ HIDS	*MVK* Chromosome 12	Autosomal recessive	Northern European	Infancy	Immunizations, infections	Diarrhoea and lymphadenopathy.	3–7 days	1–2 monthly	Elevated IgD and IgA, acute phase response, and mevalonate aciduria during attacks	Anti-IL-1 therapies, Anti-TNF therapies
FCAS	*NLRP3* Chromosome 1	Autosomal dominant	Northern European	Childhood	Exposure to cold environment	Cold-induced fever, arthralgia, rash, and conjunctivitis	12–24 h	Depends on environmental factors	Acute phase response during attacks; to a lesser extent when well	Cold avoidance, Anti-IL-1 therapies
MWS	*NLRP3* Chromosome 1	Autosomal dominant	Northern European	Neonatal/ infancy	Marked diurnal variation, Cold environment, but less marked than in FCAS	Urticarial rash, Conjunctivitis Sensorineural deafness	Continuous (often worse in the evenings)	Often daily	Varying but marked acute phase response most of the time	Anti-IL-1 therapies
CINCA/ NOMID	*NLRP3* Chromosome 1	Sporadic	Northern European	Infancy	None	Urticarial rash, Aseptic meningitis, deforming arthropathy, sensorineural deafness, mental retardation	Continuous	Continuous	Varying but marked acute phase response most of the time	Anti-IL-1 therapies

PAPA	*PSTPIP1* Chromosome 15	Autosomal dominant	Very few families reported. Northern European	Childhood	None	Pyogenic arthritis, pyoderma gangrenosum, and cystic acne	Intermittent attacks with migratory arthritis	Variable (may be continuous)	Acute phase response during attacks	Anti-TNF therapies
Blau's syndrome	*NOD2* Chromosome 16	Autosomal dominant	None	Childhood	None	Granulomatous polyarthritis, iritis, and dermatitis	Continuous	Continuous	Sustained modest acute phase response	Corticosteroids, Anti-TNF therapies Methotrexate
FCAS2/ NAPS12	*NLRP12* Chromosome 19	Autosomal dominant	Very few families reported – possibly more from Carribean	Infancy	Exposure to cold environment	Urticarial rash, sensorineural deafness, fever, abdominal pain	5–10 days	~ monthly	Variably elevated	Not well established NSAIDS, Corticosteroids Antihistamines, Anti-IL-1 therapies
DIRA	*IL1RN* Chromosome 2	Autosomal recessive	Very few families reported from various ethnicities	Neonatal	None	Fetal distress, pustular rash, joint swelling, oral mucosal lesions	Continuous	Continuous	Sustained acute phase response	Anti-IL-1 therapies
Majeed Syndrome	*LPIN2* Chromosome 18	Autosomal recessive	Very few families reported Middle Eastern kindreds	Early childhood	None	Multifocal sterile osteomyelitis, dyserythropoietic anemia, and neutrophilic dermatosis	Continuous bone inflammation, fevers for 3–4 days	Continuous, fevers every 1–2 weeks	Sustained modest acute phase response	NSAIDs, Corticosteroids, Anti IL-1 therapies
DITRA	*IL36RN* Chromosome 2	Autosomal recessive	Very few families reported – possibly more in North Africa	Variable from infancy to adulthood	Pregnancy and infections reported	Repeated flares of sudden onset generalised pustular psoriasis	Highly variable	Highly variable	Acute phase response during attacks	Unclear (Anti-TNF and IL-1 therapies)
CANDLE/ PRAAS/ NNS/JMP	*PSMB8* PSMA3, PSMA4, PSMB9 and POMP also described Chromosome 6	Autosomal recessive	Caucasian, Japanese and Asian kindreds reported	Infancy	None	Progressive partial lipodystrophy,	Continuous	Continuous	Varying but marked acute phase response most of the time	Unclear (JAK inhibition?)

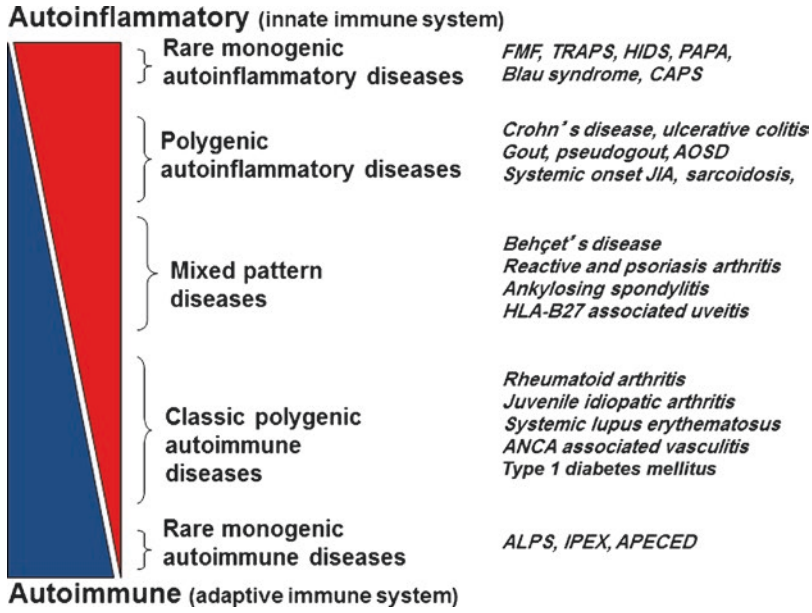

Fig. 7.1 Autoinflammatory versus autoimmune immunological diseases (Adapted with permission from [160])

symptom-free between attacks but may have subclinical inflammation.

Although the autoinflammatory syndromes have only been identified as such during the last few decades, perhaps the earliest clinical description is found in William Heberden's 1802 Commentaries on History and Care of Disease (London: T. Payne): 'Pains which are regularly intermittent, the fits of which return periodically as those of an ague; such as I have known in the bowels, stomach, breast, loins, arms and hips, though it be but seldom that such parts suffer in such a manner'. Over the last two decades the clinical descriptions have become more refined as underlying genetic causes have been identified. The first disease to have a gene isolated was Familial Mediterranean fever with the identification of pyrin mutations in 1997. Since then mutations in at least another 24 genes have been implicated in monogenetic autoinflammatory diseases with advances in understanding of their pathophysiology although there are still many unanswered questions.

Autoinflammatory diseases can be classified according to the mode of inheritance (Table 7.1). Familial Mediterranean fever (FMF), mevalonate kinase deficiency (MKD) also known as hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) and mevalonic aciduria (MVA), deficiency of the interleukin-1 receptor antagonist (DIRA), deficiency of the IL-36 receptor antagonist (DITRA), Majeed syndrome and chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome are largely autosomal recessive diseases. Tumor necrosis factor receptor-associated periodic syndrome (TRAPS), pyogenic arthritis, pyoderma gangrenosum and acne syndrome (PAPA), Blau syndrome and the cryopyrin-associated periodic syndromes (CAPS), are inherited in an autosomal dominant pattern. The concept of autoinflammatory diseases has expanded from initially including only hereditary syndromes to also encompassing non-Mendelian inherited diseases. There is still no agreement as to which of these syndromes will be included. The following diseases are often regarded as non-Mendelian autoinflammatory: periodic fever, aphtous stomatitis, pharyngitis and cervical adenitis syndrome (PFAPA), systemic onset juvenile idiopathic arthritis (SoJIA), adult-onset Still's disease (AOSD), chronic

recurrent multifocal osteomyelitis (CRMO), Behçet's disease (BD) and Schnitzler's syndrome. The role of Crohn's disease (CD) as an autoinflammatory disease or immunodeficiency is not yet settled. Apart from PFAPA, CRMO and Schnitzler's syndrome the polygenic/multifactorial diseases will only be discussed briefly.

The study of autoinflammatory diseases has given us insights into the innate immune system. Pattern recognition molecules (PRMs) are a group of molecules responsible for sensing danger signals and are involved in the first line of defense; they are highly conserved and can be seen in plants and insects. The extracellular Toll-like receptors (TLRs) were discovered in 1992. A few years later, the intracellular Nod-like receptors (NLRs) were found [93, 111] and since several other PRMs have been characterized such as Rig1 like receptors (RLRs) and C-lectin receptors (CLR). Two NLRs; Nod-like receptor family pyrin domain containing 3 (NLRP3, also known as NALP3, cryopyrin and CIAS1) and nucleotide-binding oligomerization domain protein 2 (NOD2) have been shown to be pivotal in autoinflammatory diseases [155, 238] but others have also been described, including NLR family CARD domain-containing protein 4 (NLRC4). The NLRP3 inflammasome can be activated by microbial toxins, bacterial RNA, uric acid and ATP [159]. Although, the development in the field is remarkable, much still remains to be learned regarding pathogenesis and treatment of autoinflammatory disorders.

The focus has so far mainly been on the NLRP3 inflammasome and IL-1β, but other mechanisms are also involved in autoinflammation including type I interferons and NF-κB as well as defective regulatory mechanisms with unopposed signaling [53].

The awareness and knowledge of autoinflammatory diseases is important. Patients with these diseases need to be recognized and diagnosed [122] as well as evaluated for the risk of AA amyloidosis, the main long-term risk. They should also receive appropriate treatment, with the aim of preventing episodes, inflammation and AA amyloidosis as well as improving length and quality of life.

It is often a challenge to investigate the patient with a suspected autoinflammatory disease. As in most areas of medicine, the mainstay is a good clinical case history and physical examination, in particular during episodes. Many conditions can mimic autoinflammatory diseases. Occult or recurrent infections (for example frequent viral infections, malaria, brucellosis, and *Borrelia recurrentis*) are important differential diagnosis as well as malignant diseases and atypical autoimmune diseases. Immunodeficiencies including cyclic neutropenia have to be considered. It is crucial to ascertain if there is a marked inflammatory response during attacks as this is a hallmark of systemic autoinflammatory disease. It is especially important to cover family history and ethnicity in detail. A patient diary is often valuable. The clinical picture will give a clue as to which hereditary periodic fever syndrome might cause the symptoms but there are overlaps in the clinical presentation of the different diseases. Furthermore, there are many patients with a probable autoinflammatory disease whose signs and symptoms do not fit with any of the known diseases. The understanding of these "undifferentiated" disorders need to be improved.

A proportion of patients with clinical signs and symptoms suggesting a specific autoinflammatory disease, but with no mutation found with conventional Sanger sequencing has been found to have somatic mosaicism. Most reports have been in CAPS (*NLRP3*), but somatic mosaicism has also been found in a handful of other autoinflammatory diseases.

The increased knowledge of many autoinflammatory diseases in combination with the development of cytokine inhibitors has prompted potential for better treatment.

7.2 Familial Mediterranean Fever

7.2.1 Definition

Familial Mediterranean fever (FMF; OMIM*249100) is an ancient disease but was only described as a clinical entity as recently as 1945

[220] and it was given the name FMF in 1958 [98]. FMF is the most common of the hereditary autoinflammatory diseases worldwide and prevalence of FMF has been estimated to be 1 in 250 to 1 in 500 among non-Ashkenazi Jews and 1 in 1000 in the Turkish population. The disease is mainly found in populations from the eastern Mediterranean area (especially non-Ashkenazi Jews, Armenians, Turks and Arabs). FMF can be found in other ethnic groups around the Mediterranean Sea but at a lower incidence [7, 133, 135]. It has been proposed that the only possible explanation for the high frequency of *MEFV* mutations in populations in the eastern Mediterranean area is that heterozygous carriers have a survival advantage compared to non-carrier, possibly due to an increased resistance to an undetermined infection [157]. The disease is uncommon in other ethnic populations. However, a clinical understanding of the disease has become increasingly important in other parts of the world, partly due to emigration from the eastern Mediterranean area. The disease usually presents in children or adolescents, 50 % has onset before the age of 10 years and 90 % before the age of 20 years.

7.2.2 Etiology

FMF is an autosomal recessive inherited disease caused by mutation in the MEditerranean FeVer (*MEFV*) gene (OMIM*608107) on chromosome 16. FMF was the first of the autoinflammatory diseases where a gene defect could be found (1997) [78, 112]. Initially, five mutations were described and they are still the most frequent (80–90 %). Thus far more than 300 variants have been described mostly encoding substitutions (fmf.igh.cnrs.fr/ISSAID/infevers/). Mutations in both alleles are found in only 2/3 of clinically classic cases. The reason for this is not known but mutations in another gene or in the promoter region could be explanations. *MEFV* codes for a protein, pyrin ("relation to fever") also called marenostrin ("our sea"), which is mainly expressed in granulocytes, monocytes and synovial fibroblasts. The structure and function of pyrin have not yet been characterized in detail, although it is clearly of importance for regulation of the innate immune system and subtle abnormalities of leucocyte function have been reported in FMF. The putative 781 amino acid protein has sequence homologies with a number of proteins of apparently disparate function and cellular localization. Recent work suggests that pyrin is not primarily a nuclear protein, but interacts via its N-terminal death domain with microtubules and the actin cytoskeleton, consistent with a role in directed cell migration and by the C-terminal domain to activate IL-1β and NF-κB. There are two possible mechanisms for this action of pyrin (Fig. 7.2). In the sequestration hypothesis it is believed that native pyrin has an inhibitory effect on the cryopyrin (NLRP3) inflammasome by competitive binding of ASC and pro-caspase-1 as well as binding of caspase-1 [37, 184]. The pyrin inflammasome hypothesis suggests that pyrin can form an inflammasome by binding to ASC and another adaptor protein in order to cleave pro-caspase-1 and activate IL-1β [35].

Members of the death-domain superfamily play important roles in the assembly and activation of apoptotic and inflammatory complexes through homotypic protein-protein interactions. Proteins with pyrin domains are involved in inflammation, apoptosis, and NF-κB signaling and have been implicated in pathways in CAPS as well. A recent study indicates that pyrin is activated by pathogen-mediated modifications of Rho GTPases, a small G protein that is induced by toxins from bacteria like *Clostridium difficile*, *Vibrio parahemolyticus* and *C. botulinum* [260]. This mechanism may explain the survival advantage of individuals that are heterozygous for *MEFV* in the eastern Mediterranean area.

7.2.3 Clinical Manifestations

The symptoms of FMF are self-limiting (12–72 h) recurring attacks of fever and serositis. The most frequent manifestation besides fever is peritonitis (80 %). The abdominal pain can resemble appendicitis and 40 % patients undergo laparoscopy before the FMF diagnosis is made. Pleuritis is seen in about 15–30 % of the patients [209] and is usually one-sided with painful breathing. Acute

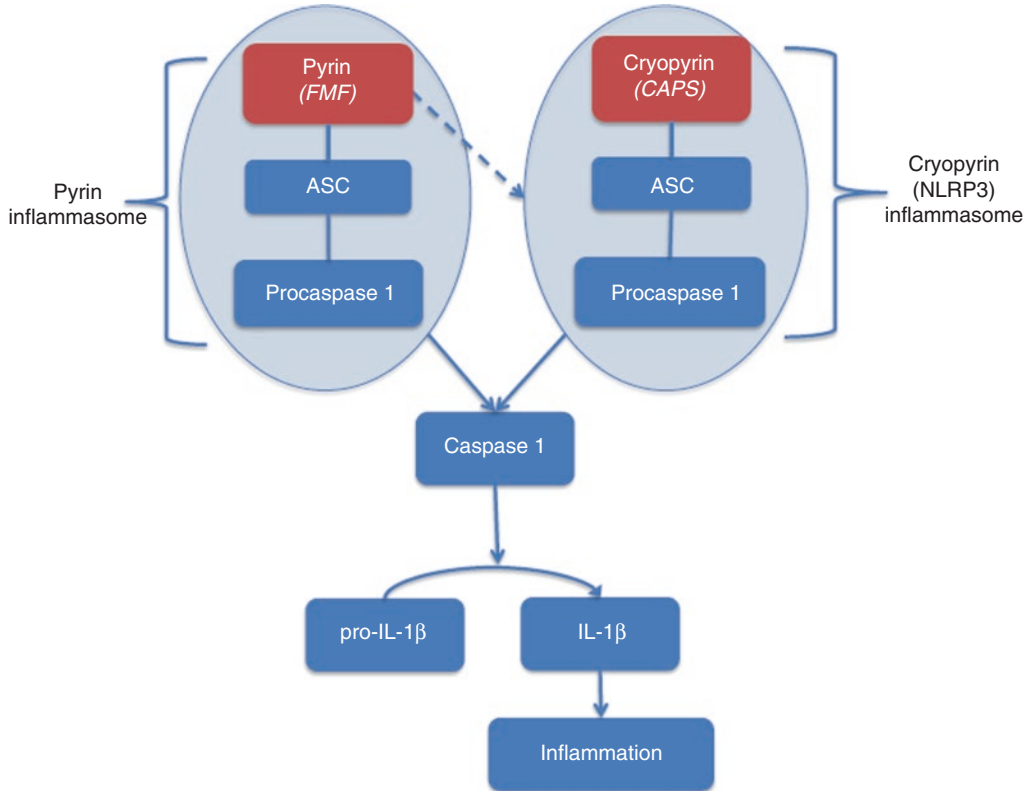

Fig. 7.2 Cryopyrin inflammasome and the pyrin inflammasome in cryopyrin-associated periodic syndromes (CAPS) and familial Mediterranean fever (FMF)

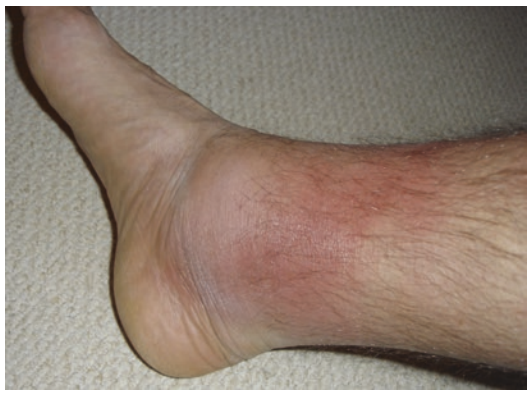

Fig. 7.3 Erysipelas-like erythema in a patient with FMF

arthritis is also common, usually affecting one or a few large joints (ankle, knee, hip or the sacroiliac joints). The arthritis is usually non-erosive but it may in rare cases be chronic and erosive. Pericarditis and orchitis can also occur but are rare. An erysipelas-like erythema during attacks is seen in about 25 % of pediatric patients [180]. The erythema is often associated with arthritis and is usually located between the knee and ankle, on the dorsum of the foot, or in the ankle region (Fig. 7.3). Polyarteritis nodosa and Henoch-Schonlein purpura are associated with FMF [243].

There is a short but marked inflammatory response during an attack indicated by an increase in CRP, ESR and serum amyloid A protein (SAA). Studies have shown that subclinical inflammation is common between attacks [65, 138], which might also affect the patients' quality of life [177].

The main risk of FMF is development of renal AA amyloidosis, which may lead to end-stage renal failure. SAA is the precursor of amyloid deposits in FMF. SAA levels rise during attacks and usually normalize in attack-free periods [244]. However, in a significant proportion of

patients, SAA levels are not normalized [65, 138]. The level of increased SAA with which there is no risk for development of amyloidosis has not been established. The *MEFV* mutation M694V and the SAA1 genotype are risk factors for amyloidosis [34, 85, 147, 265]. Interestingly, the country of residence is for unknown reasons an independent risk factor with the highest risk for those in Armenia, Turkey or Arabic countries [242]. Analysis of SAA might be a tool in diagnosing as well as monitoring FMF [17]. Patients with amyloidosis as the presenting or only manifestation of disease (phenotype II) exist but are uncommon [13, 243].

Pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND) is an extremely rare autosomal dominant disease [156]. The disease is distinct from FMF, but is caused by a mutation in *MEFV*. Manifestations include episodes of fever, dermatitis, arthralgia, myalgia and myositis.

7.2.4 Diagnosis

The diagnosis is made on the basis of clinical criteria. The Tel Hashomer criteria [148] are often used to make the diagnosis (Table 7.2). A set of criteria for childhood FMF has been proposed [261] (Table 7.3). However, these criteria have shortcomings, especially in countries with a low prevalence of FMF were the specificity is limited [131]. The diagnosis should be considered in patients with ethnicity from the eastern Mediterranean with recurrent inflammatory episodes. A diagnostic trial with colchicine treatment is part of the investigation in patients with atypical symptoms. Genetic investigation can in atypical cases verify the diagnosis but a negative mutation analysis cannot rule out the disease since *MEFV* positive mutations in both alleles are only seen in 2/3 of patients with classical FMF.

Table 7.2 Simplified criteria set for diagnosis of familial Mediterranean fever (FMF), "Tel Hashomer criteria"

Major criteria
1–4. Typical attacks
1. Peritonitis (generalized)
2. Pleuritis (unilateral) or pericarditis
3. Monoarthritis (hip, knee, ankle)
4. Fever alone
5. Incomplete abdominal attack
Minor criteria
1–2. Incomplete attacks involving one or more of the following sites
1. Chest
2. Joint
3. Exertional leg pain
4. Favorable response to colchicine

The requirements for diagnosis are ≥1 major criteria or ≥2 minor criteria. Typical attacks are defined as recurrent (≥3 of the same type), febrile (≥38 °C) and short (lasting between 12 h and 3 days)

Table 7.3 Yalçinkaya set of criteria for the diagnosis of familial Mediterranean fever (FMF) in childhood

1. Fever (axillary temperature >38 °C, duration of 6–72 h, 3 attacks)
2. Abdominal pain (duration of 6–72 h, 3 attacks)
3. Chest pain (duration of 6–72 h, 3 attacks)
4. Oligoarthritis (duration of 6–72 h, 3 attacks)
5. Family history of familial Mediterranean fever

Diagnosis is definite, if two or more criteria are satisfied

7.2.5 Management

The disease is treated prophylactically with life long colchicine [59, 90, 267]. Most patients will be symptom-free and the risk of amyloidosis is reduced from 25–40 % to less than 1 %. However, colchicine is not effective in acute attacks. Children usually need a higher dose per kilogram than adults do [123]. Colchicine can sometimes, especially in higher doses, give gastrointestinal side effects. A temporary reduction in the colchicine dose and reduced intake of lactose can relieve the gastrointestinal symptoms. Cohort studies suggest that colchicine in pregnancy is safe and should be continued. Failure to respond to colchicine should prompt a careful review of compliance but cytokine (mostly IL-1 and to a lesser extent TNF) inhibitors have been used with success in therapy resistant cases [30, 37, 94, 167, 179, 211]. Acute FMF attacks can be treated with non-steroid anti-inflammatory drugs (NSAID). Corticosteroids do not have an effect on the classical manifestations but are effective in

protracted myalgia, a rare vasculitic complication of FMF [140]. Arthritis that becomes chronic can be treated as juvenile idiopathic arthritis or rheumatoid arthritis.

7.3 Mevalonate Kinase Deficiency

(***Hyperimmunoglobulinemia D and periodic fever syndrome, Mevalonic aciduria***)

7.3.1 Definition

Hyperimmunoglobulinemia D and periodic fever syndrome (HIDS, OMIM*260920) was defined in 1984 [248] and was given its name because of increased IgD and periodic fever. Mevalonic aciduria (MVA, OMIM*251170) is a more severe disease with mental retardation and dysmorphic features in addition to similar symptoms as for hyperimmunoglobulinemia D and periodic fever syndrome (HIDS). It later turned out that both diseases are caused by a defect in the same enzyme (mevalonate kinase). The name mevalonate kinase deficiency (MKD) is now used for the both diseases, but is most often used to describe the periodic fever syndrome historically known as HIDS. MKD is an uncommon inborn error of the cholesterol biosynthesis. There are only a few hundred and less than one hundred patients known with HIDS and MVA, respectively. Most patients with HIDS are from Europe, in particular from the Netherlands and France. A common founder of the most frequent variant V377I may explain this geographical bias [222].

7.3.2 Etiology

MKD is autosomal recessive inherited and caused by a mutation in the mevalonate kinase (*MVK*) gene (OMIM*251170) located on chromosome 12 [61, 107]. The mutation leads to reduced activity of mevalonate kinase. This enzyme is part of the cholesterol, farnesyl and isoprenoid biosynthetic pathway (Fig. 7.4). In MVA, mevalonate kinase activity is almost zero [104] and in

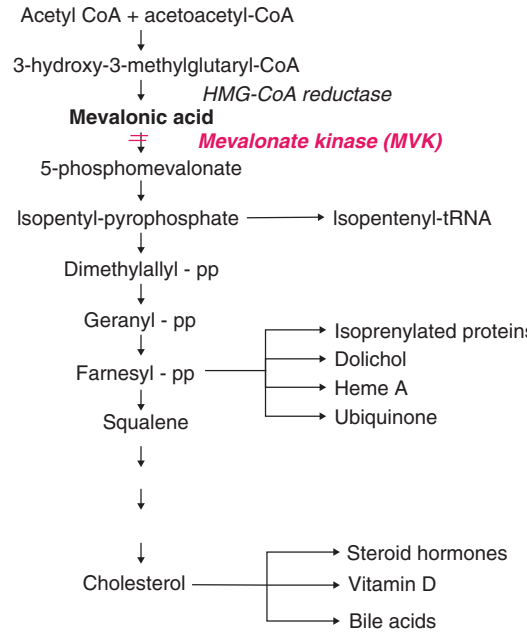

Fig. 7.4 Defect in the cholesterol biosynthesis in mevalonate kinase deficiency (MKD)

HIDS 1–10 % of normal levels [61, 107] resulting in an accumulation of mevalonic acid. In MVA mevalonic acid is continuously very high, while in HIDS it is normal between attacks and increases only moderately during attacks. There are about 60 known disease-causing mutations (http://fmf.igh.cnrs.fr/infever). HIDS is associated with a "severe" and a "mild" mutation (the most common being 1129G>A (V377I)), in contrast with MVA which is associated with two "severe" mutations. The activity of the V377I is temperature-dependent, leading to decreased activity with increasing temperature [106], which might partly explain the recurrent attacks seen in HIDS. The reason why mutations in *MVK* lead to an autoinflammatory disease is still not clear. There have been discussions as to whether the attacks are caused by an increase of mevalonate or a decrease of compounds further down the pathway (Fig. 7.4). The first hypothesis seems unlikely as an attempt to reduce mevalonate production in a patient with MVA has led to disease exacerbation [104]. Animal and *ex vivo* studies support the notion that the lack of isoprenoid triggers an IL-1β response, but the relevance of these studies need to be further explored. In any case

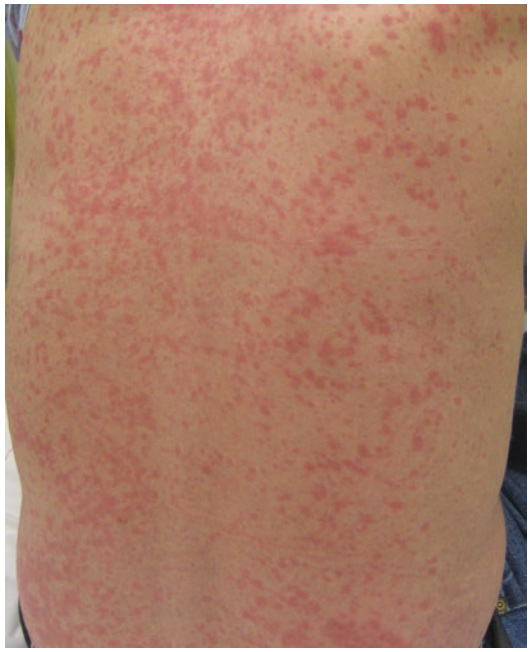

Fig. 7.5 Rash seen in a patient with hyper-IgD syndrome (HIDS) (Courtesy of A. Simon; Nijmegen, the Netherlands)

there seems to be an agreement that IL-1β has a central role in HIDS, which is supported by the clinical experience of treating patients with IL-1 blockade [246]. Another study also suggests that decreased lymphocyte apoptosis in MKD is important for the pathogenesis of MKD [21].

7.3.3 Clinical Manifestations

A continuous spectrum of clinical presentations is seen from the more benign HIDS to the severe MVA. The symptoms usually start appearing before the age of 1 year [79] and are characterized by episodes of fever and inflammation that recur every 2–8 weeks and last 3–7 days [62, 247]. Other common symptoms during attacks are skin rash, cervical lymphadenopathy, arthritis/arthralgia, diarrhea and abdominal pain (Fig. 7.5). Sometimes there are headache, and oral or genital ulcers. Retinitis pigmentosa and intermittent neutropenia have been described. The disease typically ameliorates somewhat in early adult life. Attacks in patients with HIDS can be triggered by vaccination and stress. MVA is characterized by the same inflammatory symptoms as HIDS but also by dysmorphic features, neurologic symptoms, mental retardation and failure to thrive [104].

7.3.4 Diagnosis

MKD is diagnosed by mutational analysis of the *MVK* gene. The diagnosis is supported by decreased enzymatic activity of mevalonate kinase or increased urine concentration of mevalonate [119, 246]. In HIDS, mevalonate is slightly elevated during attacks, but not during attack-free periods. It is important that the laboratory is able analyze urine mevalonate at low concentrations. Methods used for detecting aminoaciduria are not always sufficiently sensitive for analyzing the low but significantly raised levels of mevalonate in HIDS during attacks. This problem is not encountered in MVA where mevalonate is continuously very high. Acute phase reactants increase during episodes. IgD and IgA are increased in 80% of the patients both during and between attacks. The reason for the polyclonal rise in IgD and IgA is not known and does not seem to be disease specific as an increase is seen in many other inflammatory diseases including FMF and PFAPA.

7.3.5 Management

The clinical course in MKD is variable and the treatment often needs to be tailored for the individual patient. A treatment algorithm with a step-wise approach has been proposed as a tool to support clinical decisions [246]. Many patients are treated, on demand or continuously, with NSAID and/or corticosteroids [235]. Several other anti-inflammatory agents (e.g. colchicine, statins and thalidomide) have been tried without significant effect [246]. A number of case series indicate that anakinra is the most effective biological agent in MKD, with complete or partial effect in the majority of patients [235]. A smaller proportion of patients respond to etanercept, and patients that do not respond to anakinra might very well respond to etanercept or vice versa [235, 246]. Recently, a patient was reported to respond to alendronate treatment with normalization of all clinical and

laboratory abnormalities related to MKD [33]. A few patients with MVA have been treated successfully with hematopoietic stem cell transplantation (HSCT) [12, 173]. The severity of the disease seems to diminish during adulthood [64].

7.4 Tumor Necrosis Factor Receptor-Associated Periodic Syndrome

7.4.1 Definition

Tumor necrosis factor receptor-associated periodic syndrome (TRAPS; OMIM*142680) was formerly known as familial Hibernian fever due to the heredity factor and the predominance of Irish ancestry in the first cases described [256]. The disease was renamed TRAPS when it was discovered that it was caused by a mutation in the TNF receptor gene 1 [158]. TRAPS is probably the most frequent autosomal dominant hereditary autoinflammatory disease. However, it is still an unusual disease with an estimated prevalence in Europe of approximately one per million [139].

7.4.2 Etiology

TRAPS is caused by a mutation in the tumor necrosis factor receptor superfamily 1A (*TNFRSF1A*) gene (OMIM*191190) that encodes for the TNF receptor 1 (=55 kD TNF receptor). The gene for the disease, located on chromosome 12, was found in 1999 [158]. To date more than 100 different disease-causing mutations have been found in TRAPS (http://fmf.igh.cnrs.fr/ISSAID/infevers/). Two mutations, c.362G>A (R92Q) and c.224C>T (P46L), are regarded as polymorphisms or associated with a milder phenotype [195] and occur in 2 and 10 % of Caucasians and Africans, respectively. In the initial description of TRAPS it was found that there was a shedding defect of the TNF receptor, which led to decreased concentration of soluble TNF receptor in serum [158]. However, this is only true for some of the TRAPS mutations and this is probably not related to the pathogenesis. A new theory is that there is misfolding of the extracellular domain of the mutant TNF receptor 1 leading to retention in the endoplasmatic reticulum and that TRAPS may result from the consequences of the abnormally retained TRAPS mutant TNF receptor 1 [28, 149] giving rise to intracellular stress and production of reactive oxygen species.

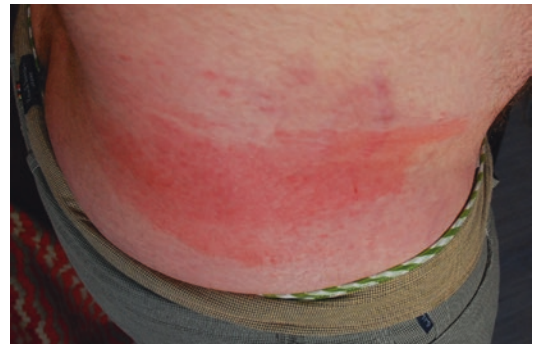

Fig. 7.6 Rash seen in a patient with TRAPS

7.4.3 Clinical Manifestations

TRAPS is characterized by long episodes (>1 week) of fever accompanied by abdominal pain, arthralgia, myalgia, skin rash, arthritis, pleuritis, conjunctivitis and periorbital edema (Figs. 7.6 and 7.7) [137]. The clinical symptoms and severity are variable. The median age of onset is 4 years but the range is wide (2 weeks to 50 years). The attacks last an average of 10 days but the duration varies from several days to more than a month. The myalgia is often migratory with an overlying rash.

7.4.4 Diagnosis

The diagnosis of TRAPS is suspected in patients with recurring long attacks (>1 week), myalgia with an overlying erythematous rash, ocular manifestations and a family history suggesting autosomal dominant inheritance. Acute phase reactants are increased during attacks. Reduced soluble TNF receptor levels are seen in many but not all patients. The symptoms of TRAPS are

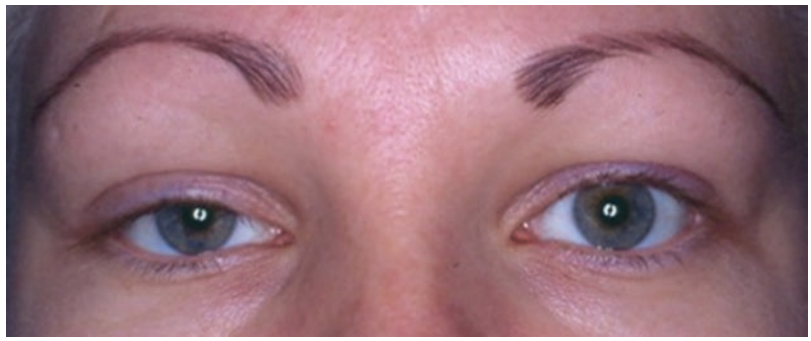

Fig. 7.7 Periorbital edema seen in a patient with TRAPS (Courtesy of T. Pettersson; Helsinki, Finland)

very variable and the diagnosis is based on DNA analysis. Somatic mosaicism, including gonosomal mosaicism, has recently been reported [206]. It is still not settled how to interpret patients with signs and symptoms of autoinflammatory disorder who have the polymorphisms (or low penetrance mutations) R92Q and P46L.

7.4.5 Management

Steroids are effective in treating TRAPS but unacceptably high doses are often required. IL-1 blockade is the current treatment of choice in patients requiring biologics [235]. Etanercept, a TNF blocking agent, has been used with some success, although not in all cases [40, 235]. Infliximab, a humanized mouse antibody to TNF, seems to be ineffective and paradoxal inflammatory reactions have been observed [63, 115].

7.5 Cryopyrin-Associated Periodic Syndrome

(***Chronic infantile neurological cutaneous articular syndrome, Muckle-Wells syndrome, Familial cold autoinflammatory syndrome***)

7.5.1 Definition

Until recently this were regarded as three distinct autosomal diseases: Chronic infantile neurologic cutaneous and articular syndrome (CINCA, OMIM*607115) also known as neonatal-onset multisystem inflammatory disease (NOMID), Muckle-Wells syndrome (MWS, OMIM*191900), and familial cold autoinflammatory syndrome (FCAS, OMIM*120100), They have now been linked to mutations in the same gene, however, and are regarded as a clinical continuum [3]. The name cryopyrin-associated periodic syndrome (CAPS), used for all three conditions, indicates that the same protein, cryopyrin, is affected in these diseases. They are all rare. It appears that MWS is more common in Europe and FCAS in North America [3].

7.5.2 Etiology

All three diseases are caused by a mutation in the NLR family, pyrin domain containing 3 (*NLRP3*) gene (OMIM*606416), The gene is located on chromosome 1. The gene for FCAS and MWS was found in 2001 [101] and for CINCA/NOMID in 2002 [5, 71]. In total more than 100 disease-causing mutations are known today (http://fmf.igh.cnrs.fr/ISSAID/infevers/). Some of the mutations are associated with part of the syndrome but overlaps are common [172]. The gene codes for a protein, cryopyrin, which is mainly expressed in neutrophiles, monocytes and chondrocytes. Cryopyrin forms a complex known as the NLRP3 inflammasome (= cryopyrin inflammasome), together with ASC and cardinal [155, 238]. This cleaves pro-caspase-1 to active caspase-1, which in turn activates IL-1β

(Fig. 7.2). The mutations in CAPS give rise to a gain-of-function of the NLRP3 inflammasome. However, the understanding of the role of the mutated cryopyrin is still unclear. There are conflicting data regarding apoptosis and regulation of nuclear factor kappa B (NF-κB) in CAPS. Not all patients with the clinical picture of CAPS (especially in CINCA but also in MWS) have a germline mutation in *NLRP3*, but somatic mosaicisms have been found in some of these patients [170, 232].

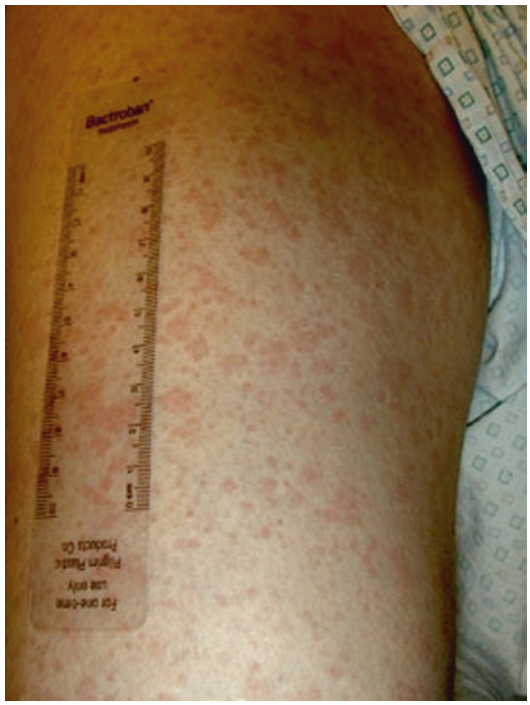

Fig. 7.8 Urticaria-like rash seen in a patient with familial cold autoinflammatory syndrome (FCAS) (Courtesy of H. Hoffman; California, USA)

7.5.3 Clinical Manifestations

Although these diseases have been classified as three different diseases they often have overlapping symptoms such as fever, urticaria-like rash, arthritis/arthralgia and an acute inflammatory reaction. FCAS and MWS are often associated with an autosomal dominant pattern of family history. The diseases can be regarded as a continuum with FCAS as the mildest form, MWS as the intermediate and CINCA as the most severe. There are overlap forms of CINCA/MWS and MWS/FCAS.

FCAS was first described in 1940 [127]. FCAS is characterized by cold-induced attacks of fever associated with urticaria-like rash, arthralgia and conjunctivitis (Figs. 7.8 and 7.9) [103]. The symptoms usually start before the age of 6 months. The average delay between cold exposure and symptoms is 2–3 h and the episode usually lasts less than 24 h. This is in contrast to the more common cold urticaria where the symptoms develop soon after cold exposure. The risk of developing amyloidosis is lower than MWS.

MWS was first described in 1962 [169]. The syndrome is characterized by episodic attacks with urticaria-like rash, fever, malaise, conjunctivitis, arthralgia and progressive sensorineural hearing loss [48, 60]. The duration of the attacks is longer (24–72 h) than in FCAS. The disease usually manifests itself during childhood but hearing loss usually begins in adolescence. About 25 % of patients will develop AA amyloidosis [1].

CINCA was first described in 1981 [190] and NOMID in 1983 [95]. It later turned out to be the same disease and the terms CINCA/NOMID are used interchangeably. In addition to fever, the

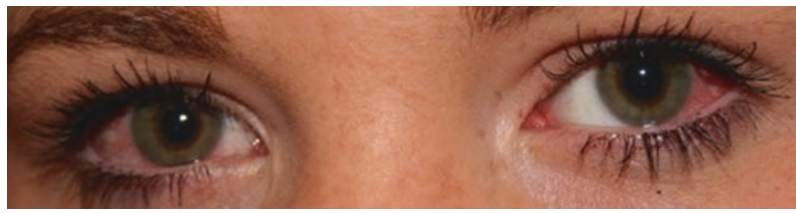

Fig. 7.9 Conjunctivitis in a patient with familial cold autoinflammatory syndrome (FCAS)

clinical spectrum includes the triad of cutaneous, neurological and articular symptoms. The non-pruritic urticaria-like skin rash usually develops in the neonatal period or in early infancy. The neurological symptoms, which vary considerably between patients, can include chronic aseptic meningitis, papilledema with optic-nerve atrophy, uveitis, seizures, cerebral atrophy, mental retardation and sensorineural hearing loss [191]. The articular manifestations differ from juvenile idiopathic arthritis by being a deforming arthropathy with bony overgrowth especially affecting the knees but also ankles, elbows, wrists and hands [191]. There is chronic inflammation with increased ESR, CRP and SAA but flares occur at irregular intervals. About 1/5 of untreated patients will not survive through to adulthood.

7.5.4 Diagnosis

The diagnosis is made on the basis of clinical criteria, see Table 7.1. Overlaps between the diseases are common and the phenotype can vary even within a family. A germline mutation in *CIAS1* is found, using conventional mutation analysis, in only about half of all cases of CINCA/NOMID [3], but somatic mosaicism seems common in "mutation negative CAPS patients" [170, 232].

7.5.5 Management

For many years, the treatment of CAPS was mainly supportive. Steroids, disease modifying anti-rheumatic drugs (DMARD) and anti-TNF therapy were used with some effect. However, a number of case reports and studies have shown substantial success in treating CAPS with IL-1 blocking agents [89, 96, 102, 136, 235]. Recovery of hearing in a patient with MWS has been reported after treatment with anakinra [166].

7.6 Blau Syndrome

(***Pediatric granulomatous arthritis, Early onset sarcoidosis***)

7.6.1 Definition

Sarcoidosis is a granulomatous multisystem disease that mainly affects patients between 20 and 40 years of age. The symptoms in adults usually involve the triad of lung, lymph node and eye manifestations. In the pediatric population two distinctive forms have been identified [204, 217]. School-aged children and adolescents have clinical manifestations similar to the adults involving lungs and lymph nodes. Young children (<5 years) usually have the triad of arthritis often causing camptodactyly, uveitis and dermatitis resulting in a characteristic tan colored rash. This syndrome is usually referred to early onset sarcoidosis (EOS, OMIM*609464). Blau syndrome (OMIM*186580), a rare autosomal dominant inherited disease with granulomatous inflammation [18, 114], was described in 1985 and the symptoms are almost identical to early onset sarcoidosis [100, 164, 204]. Sporadic early onset sarcoidosis (without a family history of the syndrome) has been shown to be the same disease as Blau syndrome [124, 125, 201]. The name pediatric granulomatous arthritis (PGA) has been proposed for both Blau syndrome and early onset sarcoidosis [203], but it has not been widely accepted. Instead, Blau syndrome is now often used for both the familial and sporadic form.

7.6.2 Etiology

Blau syndrome is caused by a mutation in the nucleotide-binding oligomerization domain protein 2 (*NOD2*) (also known as caspase recruitment domain family 15 (*CARD15*)) gene (OMIM*605956) on chromosome 16 [162]. The two most prevalent mutations are, c.1000C>T (R334W) and c.1001G>A (R334Q) [200, 203, 255]. About 20 disease-causing mutations have up today been reported (infevers, http://fmf.igh.cnrs.fr/ISSAID/infevers). The location of the mutations in Blau syndrome is in the NACTH region in contrast to Crohn's disease where mutations are found in the LRR region. The mechanism for the disease is not fully known but it is

probably involved in regulation of apoptosis and in the innate immune response to bacterial lipopolysaccharide via activation of NF-κB [201]. In Blau syndrome, there is a gain-of-function of the mutated protein in contrast to Crohn's disease where there is a loss-of-function. Studies have shown that the same mutations are found in EOS as in Blau syndrome [124, 125, 200]. These mutations are not found in older children and adults with sarcoidosis.

7.6.3 Clinical Manifestations

The dermatitis is a cutaneous eruption of small papules often described as a tan colored rash. The rash has also been described as an ichthyosis-like exanthema. This kind of rash is rarely seen in the adult form of sarcoidosis. The dermatitis can be intermittent in contrast to sarcoidosis in adults. The joint symptoms include synovitis and tenosynovitis, which often are polyarticular. Camptodactyly can develop. The most important morbidity is due to the uveitis. About 1/3 of the patients develop moderate to severe visual impairment. Bilateral panuveitis is common uveitis type and is often complicated by band keratopathy, glaucoma, and cataract formation [200].

The clinical manifestations associated with Blau syndrome are expanding [202]. In addition to the three core symptoms (arthritis, uveitis and dermatitis), fever, subcutaneous nodules, erythema nodosum, large-vessel vasculitis (early onset Takayasu disease), and several other symptoms can appear [200, 202].

7.6.4 Diagnosis

The diagnosis is supported by the clinical criteria including the core symptoms (dermatitis, arthritis, uveitis), non-caseating granulomas and onset before 5 years of age. The diagnosis can be confirmed by DNA analysis. Most patients (34/45) which are *NOD2* mutation positive have the classical triad [200]. Asymptomatic individuals with *NOD2* mutation have been reported [200]. Most, but not all patients, with the classical triad have a disease-causing mutation [125, 200, 255]. These disease-causing mutations can also give rise to atypical forms of Blau syndrome [215]. Somatic mosaicisms have been reported in patients with Blau syndrome [52, 161]

7.6.5 Management

Steroids have been used for treatment but relapses are common after withdrawal. Steroid sparing agents may be required. Case studies has shown variable efficacy with anti-TNF therapy [202]. IL-1 blocking agents seem to be largely ineffective but case reports have shown efficacy [224].

7.7 Pyogenic Arthritis, Pyoderma Gangrenosum and Acne Syndrome

7.7.1 Definition

Pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome (OMIM*604416) is an autosomal dominant inherited disease characterized by pyogenic arthritis, pyoderma gangrenosum and acne [144]. The disease is only known in a few families [43, 144, 198, 231].

7.7.2 Etiology

PAPA was mapped for a disease locus on chromosome 15 in 2000 [257, 264]. The disease was found, 2 years later, to be caused by a mutation in the proline serine threonine phosphatase interacting protein 1, (*PSTPIP1*) gene (OMIM*606347) on chromosome 15 [258]. Eleven different mutations have been associated with PAPA to date. The mechanism by which these cause inflammation is not known. However, the PSTPIP1 protein binds to pyrin, the protein affected in FMF, and may cause inflammation in the same pathway of the innate immune system as FMF [225].

7.7.3 Clinical Manifestations

The first manifestation to appear, between 1 and 16 years of age, is usually oligoarticular pyogenic arthritis [258]. The arthritis, often erosive, can start spontaneously but sometimes after a mild trauma. Usually the joint symptoms will be less pronounced with age. Acne develops later, often at puberty. The acne is often severe and cystic. Pyoderma gangranosum-like ulcerative lesions occur in some patients. Other manifestations include sterile abscesses at injection sites and pancytopenia after administration of sulfa-containing drugs. The penetrance of the disease seems to be variable and some mutation-positive family members are symptom free [56].

7.7.4 Diagnosis

The diagnosis is made on clinical criteria. The disorder should be suspected if there is a familial appearance suggesting autosomal dominant inheritance. The diagnosis can be confirmed with DNA analysis.

7.7.5 Management

There is no established treatment for this rare disorder. PAPA is only partly responsive to treatment with oral and intraarticular steroids. Case series have shown variable results on anti-TNF treatment [43, 56, 66, 226] as well as anti-IL-1 treatment [56, 58, 218, 258]. The treatment is usually more effective against the arthritis than the skin manifestations.

7.8 NLRP12 Associated Periodic Fever Syndrome

7.8.1 Definition

NLRP12 associated periodic fever syndrome (NAPS12) or familial cold autoinflammatory syndrome 2 (FACS2; OMIM*611762) is an exceptionally rare autosomal dominant disease first described in 2008 causing episodes of fever with variable associated symptoms with some reports of sensorineural deafness and cold induced symptoms [118].

7.8.2 Etiology

The nonsense and splice site mutations identified in the NLR family, Pyrin domain-containing 12 (*NLRP12*) gene (OMIM*609648) appear to reduce the inhibitory effect of the protein on NF-κB signaling [8].

7.8.3 Clinical Manifestations

Patients presented in infancy or the neonatal period with a syndrome with some features of cold induction, fever, arthralgia and myalgia, urticaria and sensorineural deafness. The first cases reported were from two unrelated families from the Caribbean and subsequent cases have been reported [23, 118, 252].

7.8.4 Diagnosis

The diagnosis is made on clinical criteria. The disorder should be suspected if there is a pattern of autosomal dominant inheritance and NLRP3 is wild type. The diagnosis can be confirmed with DNA analysis.

7.8.5 Management

There is no established treatment for this rare disorder.

7.9 Deficiency of ADA2

7.9.1 Definition

The deficiency of ADA2 (DADA2) or monogenetic polyarteritis nodosa (PAN) vasculopathy

(OMIM*615688) was described independently in 2014 by two groups [171, 270]. The clinical spectrum is wide and so far not well established. Manifestations include childhood systemic and local polyarteritis nodosa (PAN), recurrent fever, mild immunodeficiency, livedo racemosa and early-onset stroke.

7.9.2 Etiology

The syndrome is caused by recessive loss-of-function mutations in the cat eye syndrome chromosome region, candidate 1 (*CECR1*) gene (OMIM*607575), encoding adenosine deaminase 2 (ADA2) [171, 270]. The mutations cause reduced activity of ADA2 in plasma. The ADA2 protein is produced by myeloid cells and is thought to be a growth factor for endothelial cells as well as leucocytes. ADA2 deficiency may induce proinflammatory cells leading to inflammation and vasculopathy.

In contrast, overexpression of ADA2 due to gain-of-function mutation in *CECR1*, causes Cat Eye Syndrome (CES), a congenital malformation syndrome [45].

7.9.3 Clinical Manifestations

The manifestations of DADA2 are heterogeneous and the two initial case-series had different inclusion criteria. In the study by Navon Elkan et al, patients were recruited mainly from familial cases (Georgian Jewish) of PAN [171]. All the Georgian Jewish patients were homozygous for a mutation encoding p.Gly47Arg substitution.

In the study by Zhou et al., patients with recurrent fevers, livedo racemosa, mild immunodeficiency and early-onset stroke were included [270]. Six patients were compound heterozygous for eight different *CECR1* mutations. The patients with immunodeficiency had hypogammaglobulinemia/low IgM levels, recurrent bacterial and viral infections, varying degrees of lymphopenia

The three patients with PAN phenotype in this study also had homozygous p.Gly47Arg substitution.

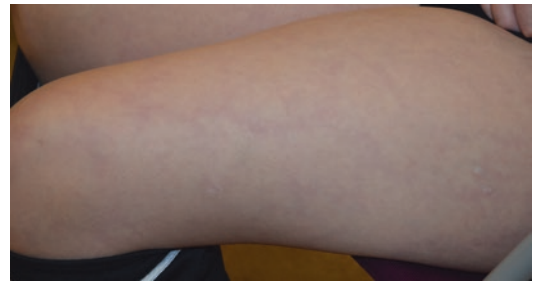

Fig. 7.10 Livedo racemosa seen in a patient with deficiency of ADA2 (DADA2)

7.9.4 Diagnosis

The diagnosis is based on clinical criteria including recurrent fever, early onset stroke, livedo racemosa (Fig. 7.10) and features of PAN. The suspicion should be especially high if there is a pattern of autosomal recessive inheritance. The diagnosis can be made by measurement of ADA2 in serum and it is confirmed with DNA analysis.

7.9.5 Management

Treatment with anti-TNF agents [171] had positive results. A few patients underwent HSCT and they are reported to have normalized their ADA2 activity and to have improved clinically [249, 250]. ADA2 replacement treatment or fresh-frozen serum could also be a possible short-term treatment option.

7.10 STING-Associated Vasculopathy with Onset in Infancy

7.10.1 Definition

The acronym SAVI (STING-Associated Vasculopathy with Onset in Infancy) (OMIM*615934) was proposed in 2014 for an autosomal dominant disorder, characterized by early-onset systemic inflammation with elevated inflammatory markers, severe cutaneous vasculopathy and lung disease [145].

7.10.2 Etiology

The syndrome is caused by a gain-of-function mutation in the transmembrane protein 173 (*TMEM173*) gene (OMIM*612374) (encoding the stimulator of interferon genes, STING) leading to an induction of type I interferon signaling [145]. SAVI is now included among the type I interferonopathies.

7.10.3 Clinical Manifestations

So far only about ten cases have been published [39]. The patients described by Liu et al ($n=6$), had onset of symptoms before the age of 2 months [145]. All had rash on cheeks, ears, nose, and digits. The symptoms of these areas worsened with time and included scarring of the ear cartilage, perforation of the nasal septa and severely affected digits. Biopsies of affected areas show vascular inflammation of the capillaries. All had fever (mostly recurrent low-grade), systemic inflammation and failure to thrive. All six had pulmonary manifestations including adenopathy, reduced lung function and interstitial lung disease.

7.10.4 Diagnosis

The disease should be considered in a child with very early onset (<2 months of age) of rash at the typical locations, fever, failure to thrive, systemic inflammation and lung involvement. The diagnosis can be confirmed with DNA analysis.

7.10.5 Management

There is no established treatment. Corticosteroids, DMARDS and biologics had no or limited effect. Treatment with JAK inhibitor (blockade of interferon signaling) is a possible option.

7.11 Deficiency of the IL-1 Receptor Antagonist

7.11.1 Definition

Deficiency of the IL-1 receptor antagonist (DIRA) or osteomyelitis, sterile multifocal, with periostitis and pustulosis (OMPP) (OMIM*612852) is an extremely rare autosomal recessive disease characterized by a neonatal onset of a pustular rash, multifocal osteitis and periarticular soft-tissue swelling.

7.11.2 Etiology

DIRA is a model of the consequences of unregulated activity of IL-1α and β in humans. It is caused by missense or deletion mutations in the interleukin 1 receptor antagonist (*IL1RN*) gene (OMIM*147679), which encodes the IL-1 receptor antagonist (IL-1Ra). Mutations in both alleles result in either complete absence or dysfunction of IL-1Ra and thus unopposed binding of IL-1α and β to the IL-1 receptors [4, 196].

7.11.3 Clinical Manifestations

The disease has been reported in only a handful of families of various ethnicities living in Northern Europe and Central America. The disease presents in the immediate neonatal period with a pustular rash, joint swelling, multifocal osteitis of the ribs and long bones, heterotopic ossification and periarticular soft-tissue swelling [4, 113, 143, 196].

7.11.4 Diagnosis

The diagnosis is made on clinical criteria. The disorder should be suspected if there is a pattern of autosomal recessive inheritance. The diagnosis can be confirmed with DNA analysis.

7.11.5 Management

Treatment is replacement of IL-1R antagonist with its recombinant form, anakinra [4].

7.12 Majeed Syndrome

7.12.1 Definition

Majeed Syndrome (OMIM*609628) was first reported in 1989 as an autosomal recessive syndrome, characterized by chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia and in some cases neutrophilic dermatosis [151].

7.12.2 Etiology

The disease was found to be due to mutations in the Lipin2 (*LPIN2*) gene (OMIM*605519) on chromosome 18 in 2005 [73]. Lipin2 is widely expressed in the liver, the kidneys, the gut, and lymphoid tissues, including the bone marrow. Lipin2 protein is thought to play role in lipid metabolism although its exact function and how mutations may cause an inflammatory phenotype is not established.

7.12.3 Clinical Manifestations

The disorder has been described in only a handful of children. Disease onset is usually in the neonatal period and attacks consist of several days of fever, severe pain, and the appearance of periarticular soft tissue swelling. Long-term complications of growth retardation and flexion contractures are well recognized.

7.12.4 Diagnosis

The diagnosis is made on clinical criteria. The disorder should be suspected if there is a pattern of autosomal recessive inheritance. The diagnosis can be confirmed with DNA analysis.

7.12.5 Management

There have been reports of modest benefit from NSAIDs and corticosteroids. Recent case reports suggest IL-1 blockade with anakinra (IL-1RA) and canakinumab is more effective although the long-term effect on dyserythropoesis is not yet known [99]

7.13 Deficiency of IL-36 Receptor Antagonist

7.13.1 Definition

Deficiency of IL-36 receptor antagonist (DITRA) or generalized pustular psoriasis (GPP) (OMIM*614204) is an autosomal recessive disease, characterized by recurrent episodes of a generalized sterile pustular rash accompanied neutrophilia, a marked acute phase response and fever.

7.13.2 Etiology

The disorder is due to mutations in IL-36 receptor antagonist (*IL36RN*) (OMIM*605507) on chromosome 2 and was identified in 2011 [152, 176]. To date 14 nonsense or deletion mutations have been described. Loss of the IL-36R antagonist is thought to result in unregulated signaling by IL-36 α, β, and γ via the Il-36 receptor. IL-36R antagonist is expressed in keratinocytes and a mouse model supports a central role of IL-36 signaling in psoriatic disease [20].

7.13.3 Clinical Manifestations

This extremely rare disease was initially reported in kindreds from North Africa and Japan with

recurrent episodes of a generalized sterile pustular rash accompanied neutrophilia, a marked acute phase response and fever. Age at onset varied from childhood to the sixth decade. Episodes could be precipitated by stress, pregnancy or drugs and they could be life threatening [69, 152, 176].

7.13.4 Diagnosis

The diagnosis is made on clinical criteria. The disorder should be suspected if there is a pattern of autosomal recessive inheritance. The diagnosis can be confirmed with DNA analysis.

7.13.5 Management

There is no established treatment for this rare disorder. Acitretin has been used with variable effect. There is one report of benefit from anakinra [205] and treatment with TNF blockade and cyclosporine have improved some patients [183].

7.14 Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature

7.14.1 Definition

The acronym CANDLE (Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated temperature) (OMIM*256040), also known as Autoinflammation Lipodystrophy and Dermatosis Syndrome (ALDO) or Nakajo-Nishimura Syndrome (NNS), was proposed in 2010 for an autosomal recessive disease, characterized by early onset, fevers, delayed physical development, microcytic anemia, recurrent annular lesions, swollen violaceous eyelids, thick lips, progressive lipodystrophy and arthralgia [240]. Therefore it could also be named as Joint contractures, Muscular atrophy, microcytic anemia, and Panniculitis-induced lipodystrophy (JMP) syndrome. The acronym proteasome-associated autoinflammatory syndrome (PRAAS) is also used as an umbrella term.

7.14.2 Etiology

The syndrome was initially described as due to substitution mutations in proteasome subunit beta type 8 (*PSMB8*) gene (OMIM*177046) on chromosome 6. Most patients are homozygote but in some cases mutations in other proteasome genes have been found [24]. *PSMB8* encodes the inducible β5i subunit of the immune proteasome. Proteasomes are ubiquitously expressed and are involved in proteolysis, generating antigenic peptides for class I MHC presentation and maintenance of cell homeostasis. It is suggested that failure of proteolysis leads to accumulation of damaged proteins, increased cellular stress and increased interferon (IFN) signaling. Cytokine profiling and analysis of the transcriptome was consistent with dysregulation of the IFN pathway in four children [2, 11, 83, 128].

Recent studies have shown that mutations in other proteasome genes (*PSMA3*, *PSMA4*, *PSMB9* and *POMP*) may also cause the disease [24]. These genes encode other subunits of the proteasome (PSMA3, PSMA4, PSMB9 and POMP). The inheritance is diallelic, but in the case of mutations in *POMP* autosomal dominant.

7.14.3 Clinical Manifestations

CANDLE was initially described in four patients with early onset, fevers, delayed physical development, microcytic anemia, recurrent annular lesions, swollen violaceous eyelids, thick lips, progressive partial lipodystrophy and arthralgia. Skin biopsies demonstrated a perivascular and interstitial infiltrate comprising mature neutrophils and atypical mononuclear cells of myeloid lineage [240]. Nakajo-Nishimura syndrome (NNS) was first described in Japan in 1939 as secondary hypertrophic osteoperiostosis with pernio and is characterized by partial lipomuscular atrophy, clubbing, a pernio-like, heliotrope-like, or nodular erythema-like rash, periodic fever and joint contractures. More than 20 cases have been reported with evidence for a common founder [11]. Joint contractures, muscle atrophy, microcytic anemia and panniculitis-induced childhood

onset lipodystrophy (JMP) syndrome was described in 2010 in three adults from a Portuguese kindred and another from Mexico [83]. It is possible that the muscle involvement and joint contractures may be later onset complications of progressive disease in untreated or partially treated patients who survive beyond childhood.

7.14.4 Diagnosis

The diagnosis is made on clinical criteria including characteristic skin histology. The disorder should be suspected if there is a pattern of autosomal recessive inheritance (N.B. autosomal dominant inheritance if the mutation is in *POMP*). The diagnosis can be confirmed by DNA analysis.

7.14.5 Management

Treatment attempts, including anti-TNF agents and the interleukin-6 (IL-6) receptor blocker tocilizumab, were only partially effective [146]. There is an ongoing clinical study (ClinicalTrials.gov Identifier: NCT01724580) of Janus Kinase (JAK) inhibitors with the aim of reducing IFN gamma-inducible protein 10 production.

7.15 Very Early Onset Inflammatory Bowel Diseases

(***IL-10 deficiency, IL-10Rα deficiency, IL-10Rβ deficiency, NFAT5 haploinsufficiency, ADAM17 deficiency***)

7.15.1 Definition

Very early onset of inflammatory bowel disease (VEO-IBD) is very rare and presents with severe enterocolitis and perianal manifestations. Extra-intestinal manifestations include recurrent fever, and often folliculitis and arthritis. The disease is autosomal recessive disease (OMIM*613148 and #612567), caused by mutations in *IL10RA* (OMIM*146933), *IL10RB* (OMIM*123889) or *IL-10* (OMIM*124092) genes [87, 88]. Recently, haploinsufficiency of *NFAT5* (OMIM*604708) has also been reported in a case with autoimmune enterocolopathy and infections [22]. Mutations in *ADAM17* gene has also been reported in two siblings of a family with inflammatory skin and bowel disease [19].

7.15.2 Etiology

There is a defect of the IL-10 axis either by loss-of-function of one of the two receptors (IL10 receptor α-chain, or IL10 receptor β-chain) or less commonly IL10. IL10 is a major anti-inflammatory cytokine that can be induced in response to colonic colonization. Decreased IL10 signaling causes a dysregulated proinflammatory cytokine response that affects macrophage activation [219].

7.15.3 Clinical Manifestations

Children develop severe inflammation in the colon and the perianal region with onset before the age of 3 months. These symptoms can be accompanied by recurrent fever, increased inflammatory markers, infections, folliculitis, arthritis, aphthous lesions. Some develops B-cells lymphoma. The patients are in a hyperinflammatory state.

7.15.4 Diagnosis

The disease should be thought of in a child with very early onset (<3 months of age) of severe inflammatory bowel disease with perianal fistules [245, 263]. Signs of autoimmunity are absent.

7.15.5 Management

Early onset inflammatory bowel disease is a severe disease and mainly refractory to standard immunosuppressant treatments. HSCT has been used as a curative treatment in small case series [68].

7.16 Autoinflammation and PLCγ2-Associated Antibody Deficiency and Immune Dysregulation

7.16.1 Definition

Autoinflammation and PLCγ2-associated antibody deficiency and immune dysregulation (APLAID; OMIM*614878) is an autosomal dominant extremely rare disease, only described in one family [268]. The disease has the uncommon combination of immunodeficiency and autoinflammation.

7.16.2 Etiology

The APLAID are caused by gain-of-function mutations in the phospholipase Cγ2 (*PLCG2*) gene (OMIM*600220). The enzyme phospholipase Cγ2 (PLCγ2) is involved in several immunological pathways and the pathway involved in APLAID is not completely understood. Activation of the NLRP3 inflammasome through Ca2+ signaling may, however, be part of the pathogenesis [36].

In contrast, another disease caused by different mutations (deletions) in the *PLCG2* gene is the PLCγ2-associated antibody deficiency and immune dysregulation (PLAID) syndrome [175].

7.16.3 Clinical Manifestations

The autoinflammatory signs and symptoms of APLAID include recurrent blistering skin lesions, interstitial pneumonitis with bronchiolitis, ocular inflammation and arthralgia. The immunodeficiency is characterized by recurrent sino-pulmonary infections.

PLAID has a different phenotype with very early-onset cold induced urticarial rash, and signs of autoimmunity instead of autoinflammation. Autoimmune features (thyroiditis, vitiligo and autoantibodies) are found in a high frequency of the patients.

7.16.4 Diagnosis

The diagnosis is made on the clinical phenotype in combination with low concentrations of IgA and IgM, and can be confirmed by DNA analysis. No autoantibodies are found. In both diseases, patients had low- or normal serum IgA and IgM levels, poor responses to pneumococcal vaccine and reduced class-switched B-cells [165].

7.16.5 Management

There is no established treatment for this rare disorder.

7.17 Sideroblastic Anemia, Immunodeficiency, Fevers, and Developmental Delay

7.17.1 Definition

Sideroblastic anemia, immunodeficiency, fevers, and developmental delay (SIFD; OMIM*616084) is an early onset disease caused by autosomal recessive loss-of-function mutations in tRNA nucleotidyl transferase, CCA-adding, 1 (*TRNT1*) gene (OMIM*612907) described in 2013 [259].

7.17.2 Etiology

TRNT1 codes for an enzyme essential for maturation of both nuclear and mitochondrial transfer RNAs. The mutations lead to metabolic defects in both the mitochondria and cytosol [38]. The mechanisms are not fully known.

7.17.3 Clinical Manifestations

The main features are severe anemia combined with recurrent non-infectious fever episodes. Most patients have B-cell lymphopenia and/or hypogammaglobulinemia. Recurrent sinopulmonary infections distinct from the recurrent fever episodes are common. Sensorineural hearing

loss, cardiomyopathy, and central nervous system abnormalities are seen in some patients.

7.17.4 Diagnosis

The diagnosis is made on clinical phenotype, and can be confirmed by DNA analysis.

7.17.5 Management

The mortality is, due to multiorgan or cardiac failure, high. There is no established treatment. Treatment with HSCT has been reported to be successful in one case.

7.18 Aicardi-Goutieres Syndromes

7.18.1 Definition

Aicardi-Goutieres Syndromes (AGS) have recently been included among the autoinflammatory diseases due to the pathogenic mechanism with increased INF type I production. AGS are discussed in detail in neurologic literature and will only be discussed briefly. AGS was initially described as an early onset progressive brain disease with pleocytosis in CSF and with basal ganglia calcifications. Beside neurologic and cognitive defects the patients may have cutaneous manifestations such as chilblain and livedo reticularis. Seven types of the syndrome have already been identified in association with type I interferonopathies [46, 47, 142] (Table 7.4).

7.18.2 Etiology

The mechanisms underlying various disease phenotypes associated with Aicardi-Goutieres syndromes have not been clearly understood. Meanwhile mutations in at least seven different genes (*TREX1*, *RNASEH2A*, *RNASEH2B, RNASEH2C, SAMHD1, ADAR*, and *IFIH1*) can cause AGS (Table 7.4). All the gene products are involved in DNA and RNA metabolism. The defect causes accumulation of nucleotides that promotes intracellular stress and results in increased type I interferon production.

7.18.3 Clinical Manifestations

Recent studies have shown that mutations in these genes may have a wide phenotype distribution, ranging from severe neurological impairment to mild cutaneous disease, systemic autoinflammation, and autoimmunity [142]. Progressive encephalopathy, intracranial calcifications, cerebral atrophy, leukodystrophy, hepatosplenomegaly are the main characteristics of Aicardi-Goutieres syndromes. Details of clinical and laboratory findings of each disease are presented in the Table 7.4.

7.18.4 Diagnosis

The diagnosis of the Aicardi-Goutieres syndrome could be made based on clinical phenotype of the patients. The main laboratory findings are thrombocytopenia, elevated hepatic transaminases, and chronic CSF lymphocytosis.

7.18.5 Management

Treatment is symptomatic and supportive, which would be done based on clinical phenotypes of disease. As some patients suffer from seizure, anticonvulsant drugs can be recommended. Special dietary advice might also be needed.

7.19 Other Monogenic Autoinflammatory Disorders

7.19.1 CARD14 Mediated Psoriasis

Most cases of psoriasis are sporadic but familial cases are described. CARD14 mediated psoriasis (CAMPS; OMIM*602723) is an autosomal dominant disease, characterized by early onset

Table 7.4 Characteristics of different types of Aicardi-Goutieres syndrome [189]

Disease	Inheritance	OMIM*	Associated features	Genetic defect	OMIM*
TREX1 deficiency (AGS1)	AR, AD	225750	Progressive encephalopathy intracranial calcifications, cerebral atrophy, leukodystrophy, hepatosplenomegaly, thrombocytopenia, elevated hepatic transaminases, CSF lymphocytosis	*TREX1*	606609
RNASEH2B deficiency (AGS2)	AR	610181	Progressive encephalopathy Intracranial calcifications, cerebral atrophy, leukodystrophy, hepatosplenomegaly, thrombocytopenia, elevated hepatic transaminases, CSF lymphocytosis	*RNASEH2B*	610326
RNASEH2C deficiency (AGS3)	AR	610329	Progressive encephalopathy, intracranial calcifications, cerebral atrophy, leukodystrophy, hepatosplenomegaly, thrombocytopenia, elevated hepatic transaminases, chronic CSF lymphocytosis	*RNASEH2C*	610330
RNASEH2A deficiency (AGS4)	AR	610333	Progressive encephalopathy, intracranial calcifications, cerebral atrophy, leukodystrophy, hepatosplenomegaly, thrombocytopenia, elevated hepatic transaminases, chronic CSF lymphocytosis	*RNASEH2A*	606034
SAMHD1 deficiency (AGS5)	AR	612952	Progressive encephalopathy, intracranial calcifications, Cerebral atrophy, leukodystrophy, hepatosplenomegaly, thrombocytopenia, anemia, elevated lactates, chronic CSF lymphocytosis, skin vascularitis, mouth ulcers, arthropathy	*SAMHD1*	606754
ADAR1 deficiency (AGS6)	AR	615010	Progressive encephalopathy, intracranial calcification, severe developmental delay, leukodystrophy	*ADAR1*	146920
AGS7	AD	615846	Progressive encephalopathy, intracranial calcification, severe developmental delay, leukodystrophy	*IFIH1*	606951

CSF cerebrospinal fluid, *XL* X-linked, *AD* autosomal dominant, *AR* autosomal recessive

plaque psoriasis or generalized pustular psoriasis [121]. It has sometimes been described as an autoinflammatory disease with local inflammation [9]

The disease is caused by mutations in the caspase recruitment domain family member 14 (*CARD14*) gene (OMIM*607211) [121]. The gene encodes CARD14 that activates NF-κB. The mutated *CARD14* is a gain-of-function mutation that further activates NF-κB. CARD14 is mainly expressed in the skin. In addition, some other rare *CARD14* variants may cause psoriasis [120].

CAMPS was initially described in only two families with early onset of plaque psoriasis and one sporadic case with generalized pustular psoriasis [121]. In contrast to many autoinflammatory disorders there is no acute phase response or fever. A recent large study could not confirm an association with familial psoriasis vulgaris but with generalized pustular psoriasis [16].

The disease should be suspected in a child with early onset generalized pustular psoriasis or plaque psoriasis. The diagnosis can be confirmed with DNA analysis.

The treatment is similar to the standard therapy for moderate to severe psoriasis.

Interestingly, mutations in *CARD14* are found in a few patients with early onset familial pituriasis rubra pilaris [80]. CAMPS and familial pituriasis rubra pilaris seems to share a similar pathophysiology and might be part of a clinical spectrum.

7.19.2 Haploinsufficiency of A20

Haploinsufficiency of A20 (HA20) or familial Behcet-like autoinflammatory syndrome (AISBL) (OMIM*616744) is a newly described disease in six families [269]. The manifestations are similar to Behçet's disease but the symptoms starts at an early age. Manifestations include oral and genital ulcers, arthritis/arthralgia, and ocular inflammation. Positive pathergy test have been described in a patient. Some patients develop autoantibodies, but autoimmune diseases seem to be rare. The disease is inherited in an autosomal recessive pattern. HA20 is caused by loss-of-function mutations in TNF alpha induced protein 3 (*TNFAIP3*) gene (OMIM*191163). *TNFAIP3* encodes A20, which is a negative regulator of the NF-κB pathway. Cells from patients have an activation of the NLRP3 inflammasome with increased secretion of active IL-1 and IL-18. Treatment with IL-1 inhibition in one patient was effective.

7.19.3 Episodic Fevers, Enteropathy, and MAS due to NLRC4 Hyperactivity

Recently two groups independently showed [31, 199] that early onset inflammatory disease with features similar to macrophage activation syndrome (MAS) was caused by a mutation in NLR family, CARD domain containing 4 (*NLRC4*) gene (OMIM*606831). The disease is very rare and these two papers described one patient and one family, respectively. The symptoms were fever and loose stool. The patients had increased inflammatory markers, hyperferritinemia, increased serum Il-18, hypertriglyceridemia, pancytopenia and splenomegaly. The disease seems to be partially responsive to IL-1 blockade.

A milder form (FCAS-like features) also with mutations in *NLRC4* have described [129].

7.19.4 TNFRSF11A-Associated Disease

In 2014, three patients with TRAPS-like symptoms (long recurrent fever episodes and abdominal pain) were found to have mutations in the tumor necrosis factor receptor superfamily member 11a (*TNFRSF11A*) gene (OMIM*603499) [117]. The gene codes for the receptor activator of NF-κB (RANK). The pathogenesis is unclear.

7.19.5 Histiocytosis-Lymphadenopathy plus Syndrome

Histiocytosis-lymphadenopathy plus syndrome (OMIM*602782) is a disease associated with histiocytosis and lymphadenopathy, caused by

homozygous or compound heterozygous mutation in the *SLC29A3* gene (OMIM*612373). Some other features such as cutaneous, cardiac, joint contractures, and/or endocrinopathy and deafness could also be seen.

7.19.6 Cherubism

Cherubism (OMIM*118400) is a rare condition, leads to prominence of the lower portion in the face, caused by heterozygous mutation in the *SH3BP2* gene (OMIM*602104).

7.19.7 Spondyloenchondro-Dysplasia with Immune Dysregulation

Spondyloenchondrodysplasia with immune dysregulation (SPENCDI; OMIM*607944) is an autosomal recessive disorder, characterized by skeletal dysplasia, metaphyseal changes and neurologic involvement [25, 197]. SPENCDI is caused by homozygous or compound heterozygous mutation in the *ACP5* gene (OMIM*171640). SPENCDI is characterized by skeletal dysplasia, metaphyseal changes, neurologic involvement, in addition to immune dysregulation [25, 197]. Recurrent bacterial and viral infections, intracranial calcification, SLE-like autoimmunity, inflammatory myositis, hemolytic anemia, and thrombocytopenia have also been reported in SPENCDI.

7.20 Multifactorial/Polygenic Autoinflammatory Diseases

7.20.1 Periodic Fever, Aphtous Stomatitis, Pharyngitis and Cervical Adenitis Syndrome

Periodic fever, aphtous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome is an acronym for the most important features of the disease i.e. Periodic Fever, Aphthae, Pharyngitis and cervical Adenitis. The first description of the syndrome was made in 1987 and the acronym, PFAPA, was established 2 years later [153, 154].

The prevalence of PFAPA syndrome is not known and the incidence has rarely been studied. In Norway the incidence has been estimated to 2.3 per 10 000 children up to 5 years of age [77]. The disease is much more common than the monogenic autoinflammatory diseases in many parts of the world, with the exception of areas with high prevalence of FMF [126]. Since the first definitions of PFAPA were established, the condition has been diagnosed, not only in children below 5 years of age, but also in older children and adults [32, 182].

PFAPA has been regarded as a non-hereditary condition [181]. However, during the years, many clinicians have experienced that one of the parents or a more distant relative had similar symptoms as a child. Familial clustering has recently been supported in the Eurofever registry, in addition to previous case series and reports [42, 212, 239]. It is only now, when children adequately diagnosed with PFAPA have children of their own that an increased familial occurrence can be investigated prospectively. A familial clustering with a non-Mendelian inheritance indicates that PFAPA is a polygenetic condition [178]. However, environmental factor(s) and multifactorial aetiology cannot be excluded, in particular when the favourable outcome of tonsillectomy is taken into account.

When a cohort of PFAPA patients was analysed for predominant mutations in classical monogenic periodic fever syndromes (i.e., *MEFV*, *TNFRSF1A*, *NOD2*, and *NLRP3*), the frequency of genetic variance was the same as in the general population [49]. Furthermore, screening for a number of autoinflammatory genes and genes coding for human inflammasomes did not detect any disease causing variants [57]. The R92Q mutation in the *TNFRSF1A* gene is regarded as polymorphism and when associated with disease the phenotype shows high rate of spontaneous resolution and amelioration of the recurrent fever episodes similar to that of PFAPA [187]. In a study from 2013 patients with PFAPA syndrome were found to have *NLRP3* variants in a significantly higher frequency than expected, but this was not confirmed in a follow-up study

[57, 130]. It has been proposed that mutations in the *SPAG7* gene could be the cause of PFAPA. However, no such conclusion can be drawn, as the child with the *SPAG7* mutation did not even fulfil the criteria of PFAPA [14].

The etiology of PFAPA remains unknown, but recent studies have shed new light on the pathophysiology. Studies of blood cell during flares demonstrate increased absolute neutrophil count as well as decreased absolute lymphocyte- and eosinophil counts [27, 130]. There are also indications that three key aspects of neutrophil function are altered in children with PFAPA, most prominently during febrile episode, including apoptosis, priming and generation of an intra-cellular oxidative burst [229]. Studies of whole blood gene expression and serum cytokines during flares indicate an activation of pro-inflammatory cytokines including IL-1β, IL-18 and IL-6 as well as an activation of INF-γ related cytokines including IP-10/CXCL10 and MIG/CXCL9 [26, 130, 228]. The question of an increased inflammatory activation between febrile episodes has yet to be resolved due to conflicting data [76, 227, 228]. Taken together the present knowledge suggests an activation of both the innate and the adaptive immune system, the latter with a likely Th-1 response [214].

The diagnosis is based on recognition of the clinical features of PFAPA. The classical criteria include periodic febrile attacks with disease onset before the age of 5 years, pharyngitis, cervical adenitis and aphthae (Table 7.5) [237]. These criteria do not exclude other conditions and needs to be further developed to improve the specificity.

The most useful discriminatory features of the disease are that the attacks are regular and appear together with signs of delineated by the acronym (including exudative tonsillitis) [84, 178]. At some phase of the disease the episodes typically occurs with an interval specific for each child, however this regularity may vanish over time [178]. The duration of febrile attacks are 3–7 days with an interval of 2–8 weeks [154, 181, 233, 237]. The fever is accompanied by pharyngitis, cervical adenitis and/or oral aphthae (Fig. 7.11). Some children have additional symptoms during the episodes including mild stomach ache, leg pain as well as nausea and vomiting [237]. Inflammatory parameters (CRP and SAA) increase markedly during attacks but normalize between attacks. The children feel well between the attacks and the symptoms usually disappear within a few years [154, 181, 237]. A clinical observation suggests that children with PFAPA syndrome have fewer viral infections than other children of the same age [237]. When the recurrent episodes disappear they seem to get viral infections at a frequency comparable to their peers.

A sometimes challenging differential diagnosis is the much more uncommon cyclic neutropenia whose exclusion is included in the classical criteria. In cyclic neutropenia, the blood neutrophils characteristically oscillate with a 21-day periodicity. When the diagnosis cannot be excluded on

Table 7.5 Diagnostic criteria used for periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome

1. Regularly recurring fevers with an early age of onset (<5 years of age)
2. Symptoms in the absence of upper respiratory tract infection with at least one of the following clinical signs:
Aphthous stomatitis
Cervical lymphadenitis
Pharyngitis
3. Exclusion of cyclic neutropenia
4. Completely asymptomatic interval between episodes
5. Normal growth and development

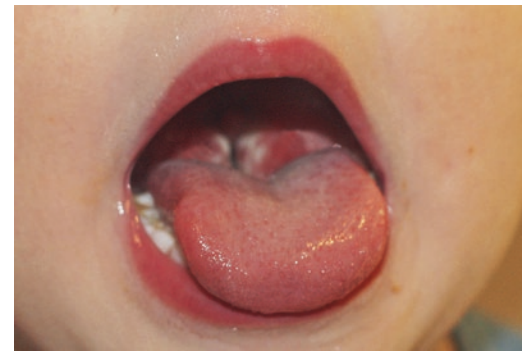

Fig. 7.11 Excudative pharyngitis in a boy with periodic fever, aphtous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome

clinical grounds, molecular analysis for the neutrophil elastase gene (*ELANE*) or repeated neutrophil counts during several weeks is recommended [50]. Recurrent infections also need to be considered, at least at the start of the disease. These include repeated streptococcal infections, and viral infections associated with tonsillitis and significant inflammation such as adenovirus. The occurrence of oral aphtae can be helpful in discriminating PFAPA from streptococcal tonsillitis. PFAPA also need to be distinguished from hereditary periodic fevers. The diagnosis should be challenged in children that fulfil the criteria if they show additional signs and symptom suggestive of monogenic hereditary periodic fevers including rash, conjunctivitis, thoracic pain, severe abdominal pain as well as episodes triggered by exercise and cold exposure [84, 213].

The treatment is mainly supportive with reduction of symptoms using primarily NSAIDs. Corticosteroids usually abort an attack within a few hours [237]. We use steroids only to postpone a febrile episode that occurs at an unsuitable time for the child, whereas others treat each episode with corticosteroids [236]. However, in a significant proportion of patients, corticosteroids shorten the interval between attacks. Colchicine has been evaluated in a few patients and need to be further investigated [234]. Tonsillectomy showed resolution of the disease in 80–90 % of cases in the initial case series [81]. These results have been repeated in a small randomised controlled trail and were supported in a Cochrane Review [29, 82]. The benefits and risks with tonsillectomy has to be assessed for the individual child, bearing in-mind the age of the child, the likely time to resolution the intensity and frequency of the episodes, as well as the quality of life and functioning of the child. One small case series indicates that PFAPA flares are responsive to IL-blockade, which has to be further evaluated [228].

7.20.2 Systemic Onset Juvenile Idiopathic Arthritis

Systemic onset juvenile idiopathic arthritis (SoJIA; OMIM*604302) is one of the categories of juvenile idiopathic arthritis (JIA) [188]. SoJIA represents 5–10 % of all JIA patients. It is the most severe category and it is a potentially fatal disease. The diagnosis of SoJIA is made on clinical criteria [188]. They include arthritis with daily fever of at least 2 weeks' duration. The typical fever pattern is fever once or twice per day followed by normal temperature and improved general condition. During the fever there is often a salmon pink evanescent skin-rash (Fig. 7.12). Generalized lymph node enlargement, hepatomegaly, splenomegaly and serositis are often present. Autoantibodies are not associated with SoJIA in contrast with several of the other categories of JIA. The etiology of SoJIA is unknown and is considered as multifactorial. However, in Saudi Arabia 5 families have been described with monogenic autosomal-recessive form of systemic JIA associated with mutation in laccase domain–containing 1 (*LACC1*) [254].

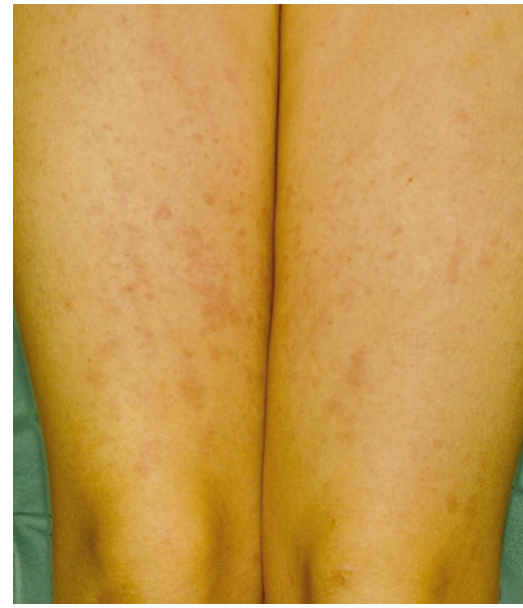

Fig. 7.12 Rash in a patient with systemic onset juvenile idiopatic arthritis (SoJIA)

Corticosteroids have been the first line of treatment and methotrexate was often used as a steroid-sparing agent. Anti-TNF treatments are generally less effective for SoJIA than other categories of JIA. A study in 2005 showed that genes involved in IL-1β processing are activated

in SoJIA [185]. Furthermore, the same study showed good results in treating patients with anakinra. Several studies has shown efficacy using IL-1 blocking agents [150, 193, 207], mainly as second line treatment. One study also showed good efficacy when anakinra was used as first line treatment [251]. The levels of IL-6 are increased in SoJIA and correlates with fever and systemic features. Studies has shown efficacy with IL-6 blockade [51, 266].

7.20.3 Adult-Onset Still's Disease

Many of the features of adult-onset Still's disease (AOSD) are similar to SoJIA [186]. AOSD is characterized by a wide variety of symptoms including intermittent fever, evanescent salmon-pink rash, arthritis, sore throat, polyserositis, lymphadenopathy, and splenomegaly. Several criteria set have been developed for AODS and the most used was developed by Yamaguchi [262]. The clinical course and severity have also a wide spectrum. Corticosteroids are used in most patients with good effect but high doses might be needed. Methotrexate can be used as a steroid-sparing agent. TNF inhibitor agent can be effective in refractory cases but are less effective than in rheumatoid arthritis [6]. Recent case-series has shown better efficacy using IL-1 blockage [86] and IL-6 blockage [41].

7.20.4 Chronic Recurrent Multifocal Osteomyelitis

Chronic recurrent multifocal osteomyelitis (CRMO; OMIM*259680) is characterized by recurrent non-bacterial osteomyelitis with or without low-grade fever [67, 75]. CRMO is a problematic diagnostic term as it is unclear how it relates, for example, to patients with a single lesion or chronic non-recurrent disease [75]. In recent years, the term chronic non-bacterial osteomyelitis (CNO) has been proposed as a unifying term that encompasses different disease progressions and number of lesions [168]. In the pediatric literature CRMO and CNO are often used interchangeably [75]. The acronym SAPHO stands for synovitis, acne, pustulosis, hyperostosis, and osteitis and is often used in adult literature [174] as it is commonly associated with arthritis and skin lesions. SAPHO and CRMO show a considerable overlap. We will mainly adhere to the term CRMO in this section.

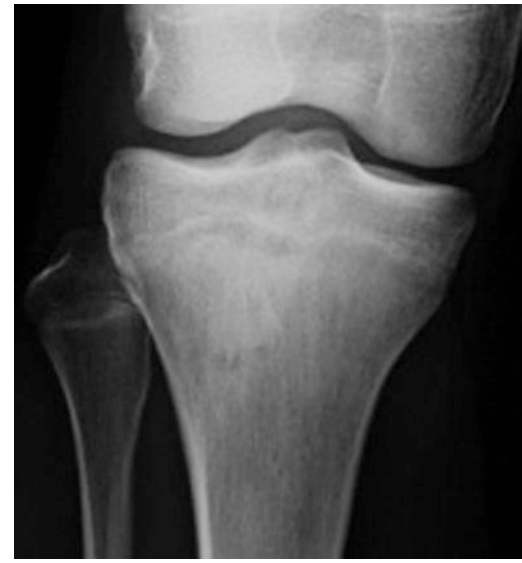

Fig. 7.13 An osteomyelitic lesion in tibia in a patient with chronic recurrent multifocal osteomyelitis (CRMO)

In addition to pustulosis palmoplantaris and psoriasis [15, 116, 141], CRMO can be associated to Sweet syndrome and IBD. There are evidences that CRMO and SAPHO can develop into ankylosing spondylitis [230, 253]. Inflammatory disorders are common in first-degree relatives (up to 50%) [74].

The diagnosis of CRMO is made on clinical criteria including no response to antibiotics and typical radiologic findings (Fig. 7.13) [216]. The location of the bone lesions are typically in the metaphyses of long bones but may also occur in the mandible, sternum, clavicle and vertebrae [108, 116] [216]. In SAPHO the osteomyelitic lesions are more often located in the anterior chest wall then it's the case in CRMO.

The etiology is unknown, but there is evidence that genetic factors may be involved due to affected family members and a report of a susceptibility gene located on chromosome 18 [91]. There seems to be

an alteration in expression of cytokines with a decrease in the anti-inflammatory cytokines IL-10 and IL-19 and an increase in the pro-inflammatory IL-20 [105]. Several monogenic diseases, with features of CRMO, have recently been discovered. Three syndromes (Majeed syndrome, PAPA and DIRA) are discussed earlier in this chapter. Interestingly diseases similar to CRMO are also seen in animals. Mutations in *PSTPIP2* cause a murine form, chronic multifocal osteomyelitis (CMO), of CRMO [72]. Canine hypertrophic osteodystrophy (HOD) is a disorder, with features similar to human CRMO that occurs especially in Weimarans [210].

The severity and the numbers of osteomyelitic lesions (1– >20) vary considerably. There are no controlled treatment trials and treatments are based on smaller case-series. The first line of treatment is often NSAID but short courses of oral corticosteroids are often needed. If failure DMARDS (methotrexate and sulfasalazine/salazopyrin) and biologics (TNF and IL-1 blockade) will be effective in many cases [97]. Bisphosphonates (pamidronate) has also been successfully used [163].

7.20.5 Crohn's Disease

Crohn's disease (OMIM*266600) is an IBD, characterized by an often relapsing transmural, granulomatous inflammation. It is sometimes associated with arthritis and skin manifestations. The disease is associated with *NOD2* mutations [109]. However, the mutations have a different location than in Blau syndrome and are probably associated with a loss-of-function in contrast to Blau syndrome where a gain-of-function is seen. There are conflicting results regarding the role of the *NOD2* mutations in the pathogenesis of CD [192, 194].

7.20.6 Behçet Disease

Behçet Disease (BD; OMIM*109650) is a chronic relapsing multisystemic inflammatory disease that has been suggested to be included among the autoinflammatory syndromes [92] even if some features, such as HLA association, resemble an autoimmune condition. The disease is mainly found in populations around the "Silk Route". The hallmarks of BD are recurrent oral and genital ulcerations, uveitis, and heterogeneous skin lesions (folliculitis or erythema nodosum) [208]. Other manifestations include musculoskeletal, gastrointestinal and neurological symptoms. Some patients have a pathergy phenomenon.

The classification criteria from 1990 are often used [44]. Mutations in the *MEFV* gene, responsible for FMF, are found in a high frequency in BD [241] but there are no increases in *MVK*, *NLRP3* or *PSTPIP1* mutations [132]. The treatment depends on the severity and organs involved. Treatment may include corticosteroids, colchicine, azathioprine, thalidomide and biologics (TNFα or IL-1 inhibition) [10].

7.20.7 Schnitzler Syndrome

This was first reported in 1974 and is characterized by a chronic urticarial like rashes (Fig. 7.14), a monoclonal immunoglobulin M (IgM) immu-

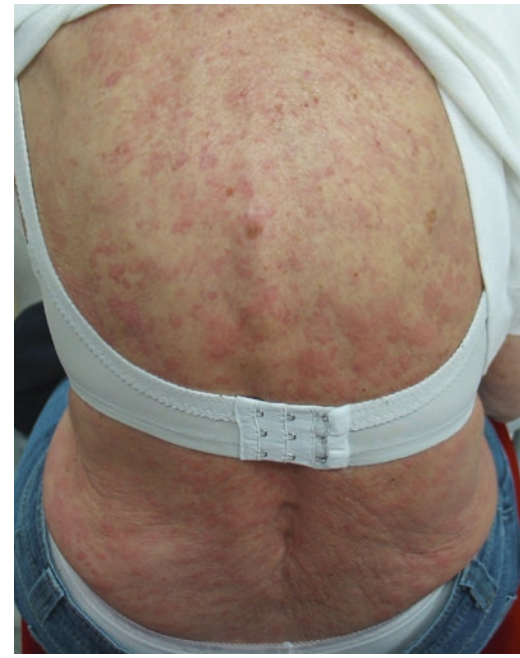

Fig. 7.14 Chronic urticarial-like rash seen in a patient with Schnitzler's syndrome

nopathy and systemic inflammation usually presenting as fever [221]. The median age at onset is 51 years and there is a slight male preponderance. The monoclonal protein appears central to the pathogenesis although the mechanism remains unclear. About a fifth of patients eventually progress to overt plasma cell malignancy. Chemotherapy has been used in the past but does not appear to relieve the syndrome and should only be used for conventional hematological indications. The treatment of choice of Schnitzler's is IL-1 blockade [54, 55, 134].

7.20.8 "Undifferentiated" Autoinflammatory Disorders

Many patients with suspected autoinflammatory disease do not fit in any of the above-mentioned syndromes. This is a diagnostic and treatment challenge. Only a few percent of patients in this category have been found to have an "autoinflammatory" mutation [70, 223]. It is important to follow these patients, in particular regarding the risk of renal amyloidosis, the severe complication of autoinflammatory diseases. It might be advisable to follow creatinine, SAA and check for proteinuria. In case of persistent inflammation a therapeutic trial with anti-inflammatory agents (colchicine, corticosteroids or biologics) should be considered.

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